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REVIEW ON GASTRORETENTIVE DRUG DELIVERY SYTEM

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Abstract:

The oral delivery system is the mostly preferable route of drug delivery because easy to administered, non-evasive in nature, flexibility in formulation and patient compliance. Gastro retentive drug delivery system (GRDD) improve the bioavailability of drug, therapeutic efficacy and reduce the dosing frequency. Drug absorption in GIT is a high variable procedure and such it depends upon the factors like absorption of drug on site, drug release from the dosage form, gastrointestinaltransit time of dosage forms and gastric emptying process.gastroretentive dosage forms remain in the gastric region for longer periods and prolonged gastric retention time of the drugs. one of the important approach of gastroretentive drug delivery system such as prolong gastric residence time, thereby targeting site specific drug release in the stomach.[4] when mechanism of gastroretentive floating drug delivery system that the formulation are prior to the administered in solution form after the administered solution contact with gastric fluid in stomach they form gel and float on the gastric fluid. The gel are float on gastric fluid in the longer period of time. We have reviewed in this various approaches of gastroretentive drug delivery system, advantages, disadvantages, mechanism of drug delivery and other.

Keywords: *Gastroretentive Drug Delivery System, Floating system, Non floating system, Microspheres.*

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INTRODUCTION:

The oral delivery system is the mostly preferable route of drug delivery because easy to administered, non-evasive in nature, flexibility in formulation and patient complience. They are immediate release on site specific,from oral drug delivery progress now a day. [**1-2]**Most orally administered drugs show poor bioavailability when administered as a solid dosage form, i.e. the rate and extent of drugs are absorbed is less than desirable. it is difficult to predict the actual*in vivo* release time of oral controlled release dosage form.[**2]**Gastro retentive drug delivery system(GRDD) improve the bioavailability of drug, therapeutic efficacy and reduce the dosing frequency. Drug absorption in GIT is a high variable procedure and such it depends upon the factors like absorption of drug on site, drug release from the dosage form, gastrointestinaltransit time of dosage forms and gastric emptying process.gastroretentive dosage forms remain in thegastric region for longer periods and prolonged gastric retention time of the drugs. The release of drug in stomach will be controlled manner, that why the drug supplied continuously to absorption site in Gastrointestnaltrac ti.e.stomach.**[3]**one of the important approach of gastroretentive drug delivery system such as prolong gastric residence time, thereby targeting site specific drug release in the stomach.[**4]** when mechanism of gastroretentive floating drug delivery system that the formulation are prior to the administered in solution form after the administered solution contact with gastric fluid in stomach they form gel and float on the gastric fluid. The gel are float on gastric fluid in the longer period of time**[.5]**

Physiology of GIT

The anatomy and physiology of Gastrointestinaltract (GIT) it must well known prior developing Hydrodynamically Balance System (HBS). The factors affecting GI like pH, nature, gastric mucosa and volume of gastric secretion **[6]**. The stomach is divideded as a 3 parts: fundus body and antrum (pylorus). The Proximal part made by fundus and body region, undigested substances reserve in proximal part of body. The distal region (antrum) is site of mixing action or distal region act as pumps for gastric emptying **[7]**. Gastric emptying is depends on fed and fasted state of stomach. The mucus, saliva and debris are mostly present in fasted state of the stomach. intra gastric series of cyclic contractions are characterize by fasted state and electrical events takes place, it is called as migrating myloelectrical cycle (MMC) or interdigestive migrating myloelectric complex. This cycle occurs in both intestine and stomach on every 2 To 3 hrs**[8-9]**. MMC is divided as four phases described by Wilson and Washington **[10-11]**. The internal view of stomach is shown in Figure 1.

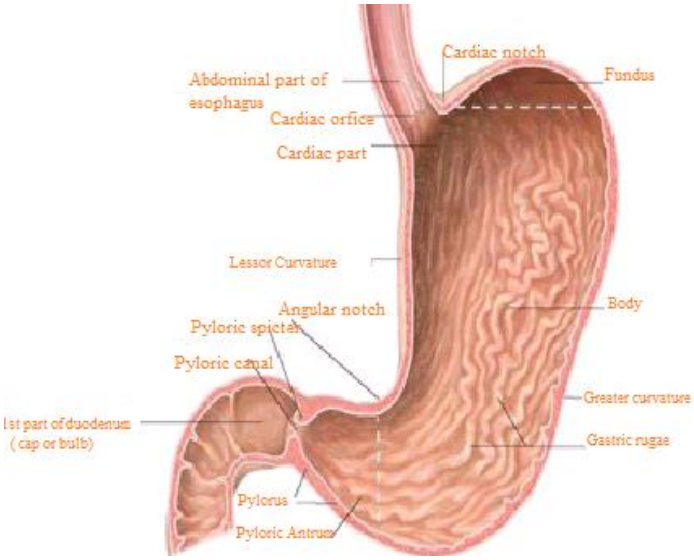

Fig. 1: Diagrammatic representation of internal view of stomach

- **Phase I**(basal phase): period which lasts from 30–60 min.
- **Phase II** (preburst phase): this phase mainly increases frequency and intensity for progress of phase and period about 40-60 min.
- **Phase III** (burst phase): This phase is short period of intense, larger distal and proximal gastric contractions (4 To 5 per min) period about 4-6 min. Burst phase is also called as "house keeper wave", burst phase sweep undigested gastric contents from stomach to intestine [11-12].
- **Phase IV**: transitionalof phase about 0 To 5 min, this phase occurs between the last part of phase III and starting of phase I. After feeding, phase IV cycle leads to changing contractions pattern, may last for many min. increase gastric retention time because of the frequently feeding of mixed meal [13-14]. The details of phases are shown in Figure 2

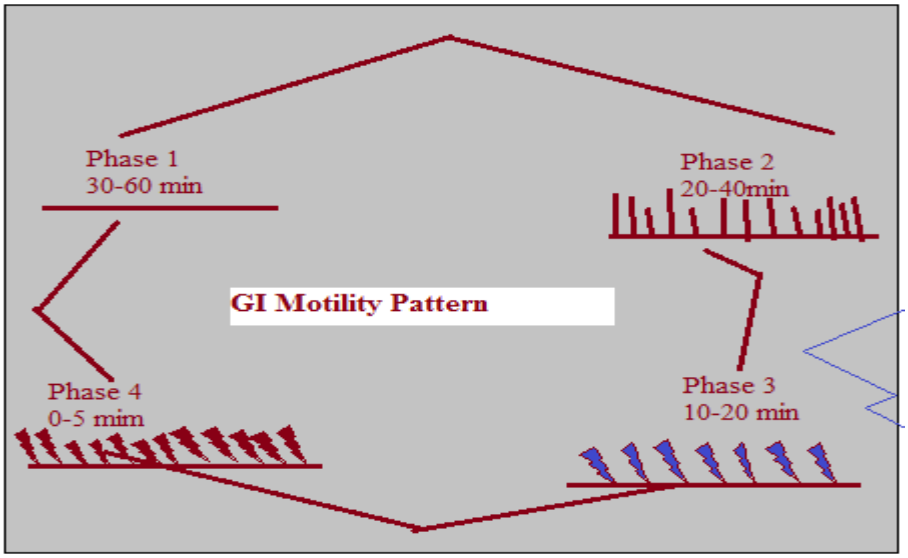

Fig. 2: Typical GI motility pattern in fasting state

Contractions pattern will be changes from fasted to fed state, after the ingestion of mixed meal. This is also called as digestive motility pattern and continuous contractions comprise in phase II of fasted state. These contractions leads to reduce size of food particles (≥ 1 mm), the study determining the gastric emptying rates of orally administered controlled release dosage forms are basically occurs two problem such as short unpredictable gastric emptying rate and gastric residence time.

Factors affecting gastric retention [15,16,17]

There are many factors that affect gastric emptying of an oral dosage form, viz.

- **Density**: buoyancy of dosage form mainly depends upon the Density. Gastric Resident Time is main function of the buoyancy.
- **Size**: diameter of dosage form more than 7.5 mm they are reported to have an increased the Gastric Residence Time compared with a diameter of 9.9 mm.
- **Shape:** Tetrahedron and ring shaped devices are reported to have better Gastric Residence Time ≈ 89% to 100% retention at 24 hrs compared to other shapes.
- **Fed or unfed state**: GI motility is characterized in fasting condition for periods of strong motor activity or migrating myloelectric cycle occurs at every 1.5 - 2 hrs. The Gastric Residence Time of unit expected as a shorter. Thus, in under fed state, Migratingmyloelectric cycle can be delayed and Gastric residence time can be longer.
- **Nature of meal**: motility pattern of stomach of fed state can be changed after the feeding of indigestible material and fatty acid salts, they can decrease gastric emptying rate and prolong the release of drug.
- **Caloric content**: feed the meal with high proteins and fats can be increased gastric residence time (3 to 10 hrs)
- **Frequency of feed**: when meals are given compared with a single meal of less frequency of Migratingmyloelectric cycle can be increase the Gastric residence time for 6 to 7 hrs.

Biological factors such as[18,19,20]

- **Gender:** GRT of males (3.4±0.6 h) is less compared with their age and female GRT of (4.6±1.2 h), depends on the height, weight and body surface.
- **Age**: over the age of 70 (Elderly people) have a greater GRT, women and old people have short gastric emptying rate as compared to men and younger people.
- **Posture**: in between supine and upright ambulatory states of the patient can vary the GRT
- **Concomitant drug administration**: Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride; and Diabetes and Crohnsdisease.

In addition to this,Regular body exercise may also influence gastric emptying .

Location of various gastroretentiveformulation in stomach shown in Figure 3.

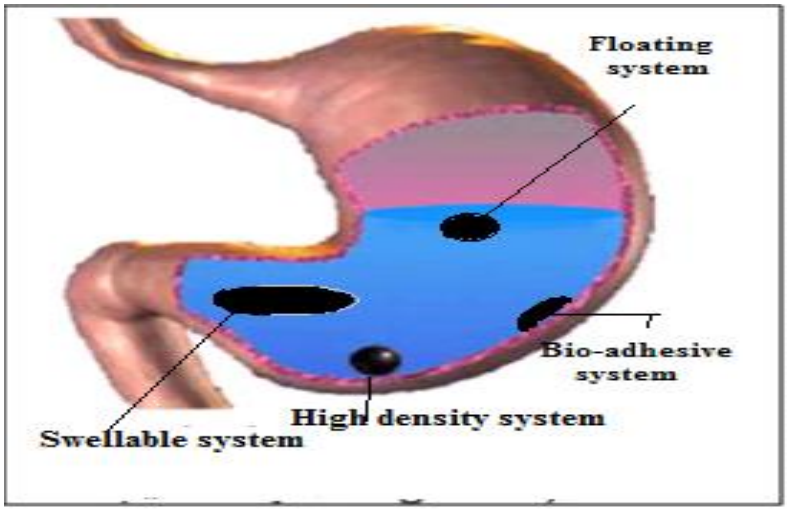

Fig. 3: Various gastroretentiveformulations in the stomach

Advantages of Gastric floating drug delivery systems (GFDDS) [3,4, 21]

- Gastroretentive drug delivery system delivers the drug with narrow absorption window in small intestine site.
- GRDDS improve the bioavailability of a poor drug absorb in a Gastrointestinal Tract such as lisinopril, ranitidine,captopril and some antibiotics etc
- Gastroretentive Drug delivery system is site specific drug delivery system
- GRDDS is controlled drug delivery system and reduce the dosing frequency of drug and plasma drug concentration profile.

Disadvantages of Gastric floating drug delivery systems (GFDDS) [3, 22]

- Gastroretentive Drug Delivery are not suitable for the aspirin and NonsteroidAni Inflammatory Drug.
- Gastroretenive Floating Drug Delivery System is not desirable for those drug have stability and solubility problem in Gastrointstinal Tract.
- Gastroretentive Drug Delivery System can't deliver drug that have a stability problem in acidic environment and low solubility in acidic environment.

Mechanism of drug release from GFDDS [23]

During the release of drug different mass transport process occurs from polymer based matrix system, including

1) Imbibition of gastric fluid in the system,
2) swelling of polymer,
3) dissolution of drug,
4) Diffusion of drug in outer part of capsule and
5) dissolution of polymer.

Above mention important process based on the types of drug, polymer, dissolution medium and dosage form composition. As per Figure 4

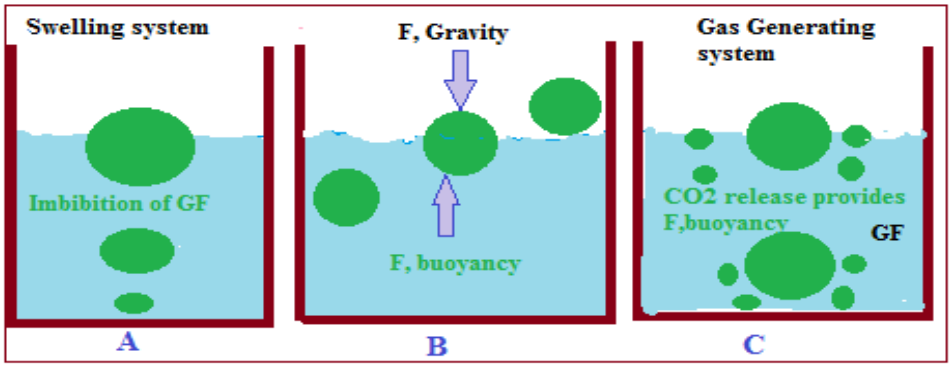

Fig. 4: Mechanism of drug release from GFDDS

Practical approaches for designing floating drug delivery systems (FDDS)

1 Non-Effervescent FDDS

a. Low density floating systems
b. Swellable and expanding systems
c. Bioadhesion systems
d. Modified shapes systems
e. High density systems
f. Delayed release gastric emptying approaches
g. Microballoon/ Hollow microspheres
h. Magnetic systems

2 Effervescent FDDS

a. Effervescent system (tablets, capsules and granules)
b. Raft forming systems
c. Programmable drug delivery systems
d. Gas generating system

3 Intragastric floating drug delivery system

1 Non-effervescent FDDS

It works on the mechanism of polymer swelling, bioadhesion of the polymer to mucosal layer of GIT. The commonly used polymer for the preparation of non-effervescent FDDS of gel forming or swellable type hydrocolloids, matrix forming polymers and polysaccharides likebioadhesive polymer like carbopol and chitosan polymethacrylates, polycarbonates and polyacrylates polystyrenes.**[24-25]**.

a. Low density floating systems[26-27]

Low density floating system is also called as hydrodynamically balanced systems (HBS) or floating drug delivery systems (FDDS).Have a low bulk density than gastric fluid, i.e. ≥1 g/cm3. Approximately specific gravity of gastric fluid is1.004 to 1.01g/cm3. Commonly used gel-forming hydrophilic polymers like hydroxypropyl cellulose (HPC), Hydroxypropyl methylcellulose (HPMC), sodium carboxymethyl cellulose (NaCMC), hydroxyethyl cellulose (HEC), polycarbophil, polyacrylate, polystyrene, agar, carrageenans or alginic acid. As shown in Figure 5.

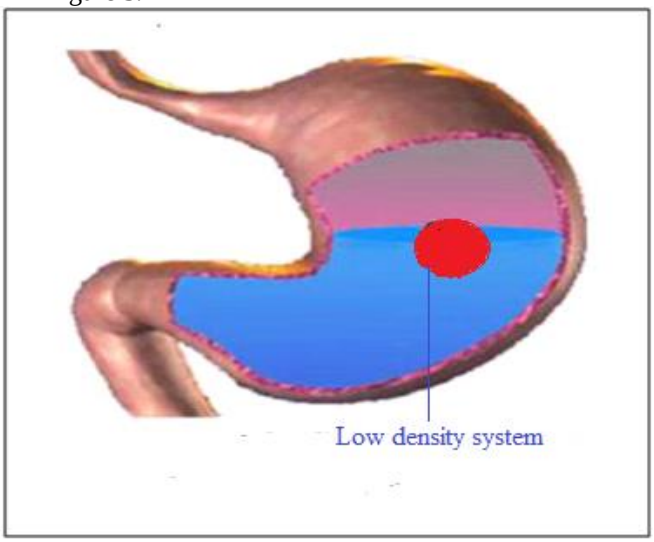

Fig. 5: Schematic localization of low density system in the stomach

b. Swelling and expanding systems [25]

These systems are such that after administration they swell to that extent which prevents their exit from stomach through pyloric sphincter. As a result, the dosage form is retained in stomach for long period of time. Swelling systems referred the plug type systems because they are tend to always on the pyloric sphincter. Diagrammatic representation shown in Figure 6

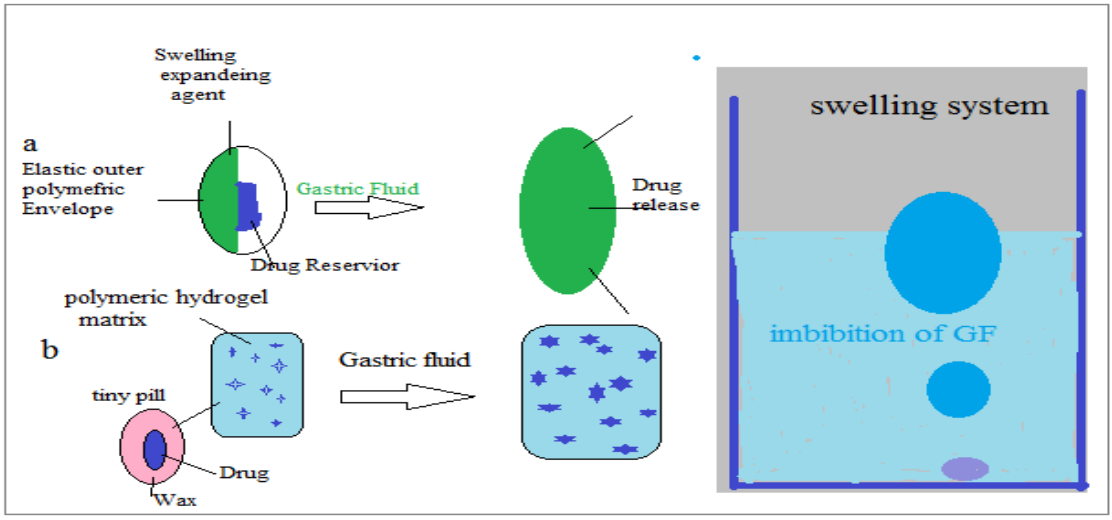

Fig.6: Swellable drug delivery systems

c. Bioadhesive Systems

Bioadhesivesystems are always used to delivery device locate on the lumen and cavity of the body for the enhance the absorption of drug on the specific site. achieved better bioadhesive on specific siteused various grades of bioadhesive polymer for this manner. Bioadhesivepolymer form the hydrogen and electrostatic bondon the mucus membrane. When they contact with e muco-epithelial surface they form faster hydration. **[28]**

d. Modified shape systems

Modified shapesystem are non-disintegrating geometric shapes made by the plastic elastomer and this extruded from the blends of polyethylene this are leads to extend the Gastric Residence Time, its based on the size, shape and flexural modulus of drug delivery system **[29]**

e. High density formulations [30]

In which high density formulation have the greater density than the stomach content.This approach can be achieved by using barium sulphate, zinc oxide, titanium dioxide and iron powder(heavy inert material) coated by drug. As per Figure 7

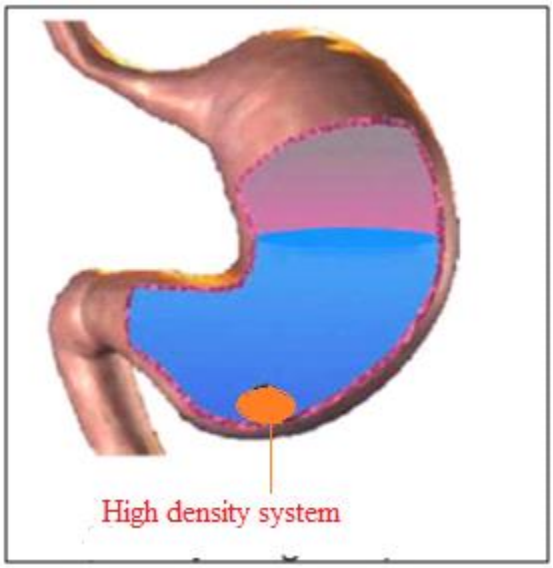

Fig 7: Schematic localization of a high density system in the stomach

f. Delayed release gastric emptying approaches [25]

Motility pattern of the stomach can be changed feeding of the indigestible material and fatty acid salt and decrease gastric emptying rate.

g. Microballoon / Hollow microspheres and Microparticles

Using simple solvent evaporation or solvent diffusion evaporation method were prepared by drug loaded hollow microsphere / Microballoons to prolonged gastric retention time (GRT) of dosage form. Mainly used polymer to developed these system such as calcium alginates, Eudragit S, low methoxy pectin, polycarbonate, cellulose acetate, agar etc.

The various floating preparations include hollow microspheres (microballoons),powder, capsule, pills, granules and laminated films. Mostly reported floating system in literature are single unit systems, likehydrodynamically balanced systems and floating tablets. But these system are not suitable for prolonging gastric residence time in the stomach when orally administered.**[31]**

h. Magnetic systems

Magnetic system based on a dosage form contains a small internal magnet and this magnet are placed in abdomen over the position of the stomach. Rouge and co-workers showed the multiple unit dosage forms decreases the inter-subject variability in absorption and minimizes probabilities of dose dumping by uniform distribution within the gastric content and provides longer duration of action.**[32]**

2 Effervescent FDDS

a. Effervescent systems (tablets, capsules and granules)

These matrix system achieved by using swellable polymers like polysaccharides, hydroxypropyl methylcellulose and chitosan**[34]** and many effervescent components such as citric acid, calcium carbonate, sodium bicarbonate or tartaric acid. These dosage forms developed by, formulation come in contact with gastric fluid in the stomach, CO2 is release and trapped in the swollen hydrocolloids. Thiswill be provides buoyancy of dosage form. The liberated carbon dioxide may intimately get mixed within the tablet matrix in case of single layered tablet **[35]**. The multiparticulate floating reservoir types of delivery systems may contain double or triple layers. Triple layer tablet prepared using swellable gas generating layer. Floating and pulsatile drug delivery system depends on effervescent core and the development of this system based on the sustainable approach. Effervescent systems shown in Figure 8.

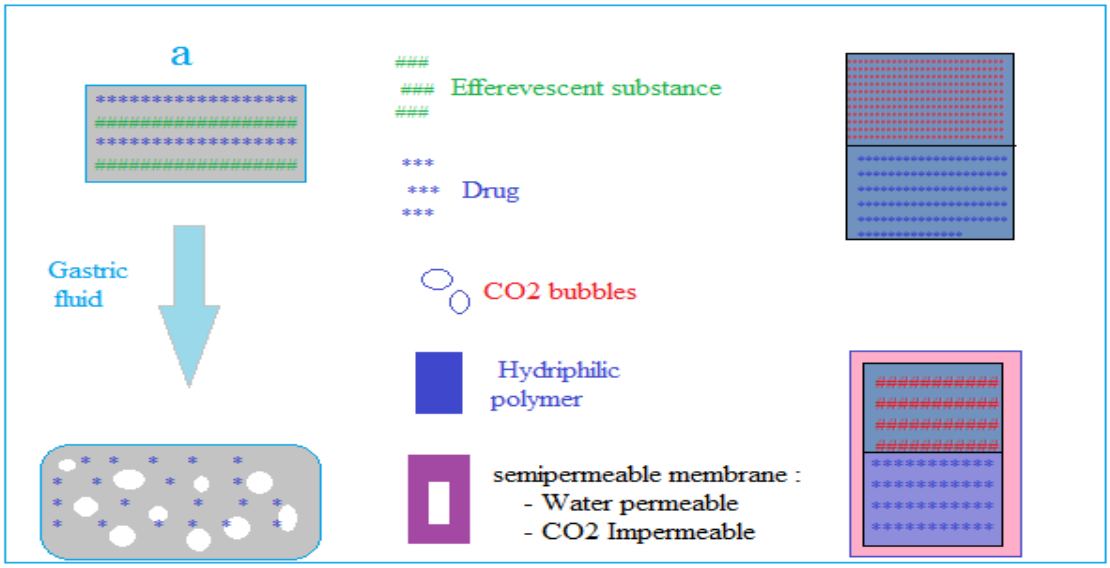

Fig. 8: Schematic representation of gas-generating systems as monolayer drug delivery system

b. Raft forming system [36,37]

The drug delivery by Raft forming systems used to cure gastrointestinal infection and GI disorder i.e Antacid. This raft buoyancy on gastric fluids because of low bulk density polymer they form the CO2. In this system a gel forming agent, carbonates and alkaline bicarbonate they are used for the formation of CO2 to floating of formulation on the gastric fluids in stomach. This system contains a gel forming agent (alginic acid), acid neutralizer and sodium biocarbonate, they forms a foaming sodium alginate gel (raft) after in contact with gastric fluids. The raft forms floats on the gastric fluid and prevent the reflux of gastric conten i.e. gastric acid. Esophagus act as a barrier in between the esophagus and stomach shown in the shown in the Figure 9.

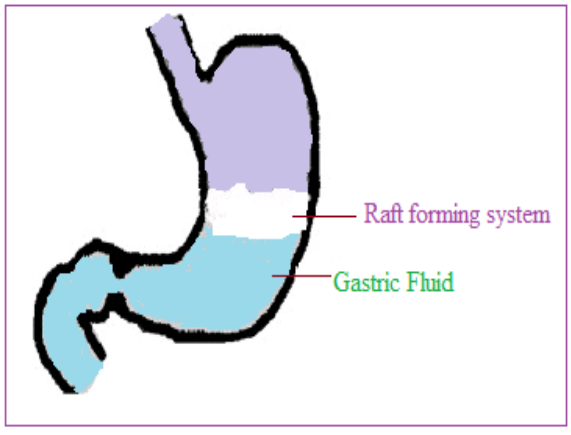

Fig.9: Schematic illustration of the barrier formed by a raft-formingSystem

c. Programmable drug delivery systems[38]

This is new device 3 cm in long and 0.9 cm in internal diameter.it is made by comprising of a cylindrical shell they form of oral capsule. made by the slowly eroding polymer after the drug was place on cylindrical disc and they are compressed the flexible rubber disc,zero porosity, acid resistant spring and a special acid impervious non-permeable rubber ballooning system containing bicarbonate granules. This device is form the non-digestible oral capsule containing the drug in slowly erodible matrix was designed to utilize on automatically operated geometric obstruction that keeps the device buoyancy in the stomach and they are prevents the system passing through the GIT. When various grades of HPMC(Hydroxypropyl methyl cellulose) were used to develop the eroding matrix.

d. Gas generating systems [39]

These systems floating on gastric fluid and contain matrices prepared by using:

1. Swellable polymers such as hydroxypropyl methylcellulose (HPMC).
2. Polysaccharides such as chitosan.
3. Effervescent components such as tartaric acid, citric acid and sodium bicarbonate.

ratio of sodium bicarbonate and citric acid should be 1:0.76 and this ratio used For the preparation gas generating system, firstly resin beads are loaded with bicarbonate and then coating with ethyl cellulose is done. When coating is insoluble in water but they are

allowsto permeat the water through it. That's why liberate the CO2 and beads floating on the gastric fluid. Mainly used polymer for these systems such as carbopol, agar, calcium chloride, HPMC, polyvinyl acetate, polyacrylate polymers, sodium alginate, polyethylene oxide, and polycarbonates. Diagrammatic representation was shown in Figure. 10.

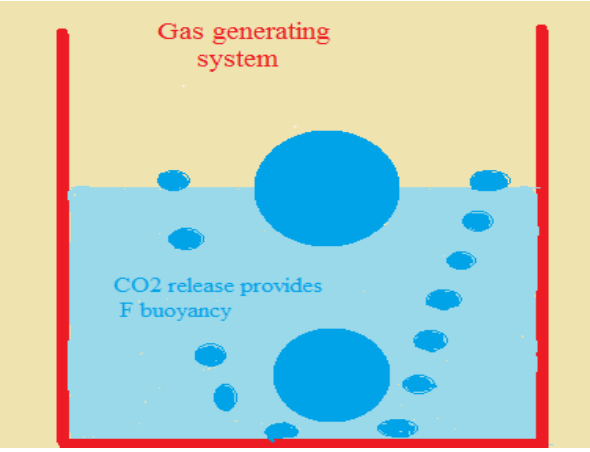

Fig. 10: Gas-generating systems

CONCLUSION:

Gastroretentive drug delivery system most commonly used now a day.Gastroretentive floating drug delivery system most extensively used to deliver the drug have an narrow absorption window and gastric region site.Gastroretentive drug delivery have an advantages to enhance the bioavailability of poor drug, patient compliance and reduce the fluctuation of plasma drug concentration profile of the drug. Drug absorption in GIT is a high variable procedure and such it depends upon the factors like absorption of drug on site, drug release from the dosage form, gastrointestinal transit time of dosage forms and gastric emptying process.

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